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ORIGINAL ARTICLE

Discrepancies between creatinine-based and cystatin C-based equations in estimating prevalence of stage 3 chronic kidney disease in an elderly population

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Background. The prevalence of stage 3 chronic kidney disease (CKD) is increasing, calculated using the modification of diet in renal disease (MDRD) study equation for estimating glomerular filtration rate (GFR). Cystatin C-based equations are also being used to estimate GFR. Using creatinine-based and cystatin C-based equations, the aim of our study was to measure the difference in prevalence of stage 3 CKD in a population. **Methods.** CKD screening is organized in the Province of Liège, Belgium. On a voluntary basis, people aged between 45 and 75 years are invited for screening. GFR is estimated using the MDRD study equation and by the three recent cystatin C-based equations proposed by Levey's group. The Levey 1 equation is based on cystatin C only and the Levey 2 equation on cystatin C corrected for age and sex. The Levey 3 equation combines cystatin C, creatinine, age and sex. **Results.** The population screened comprised 754 people. Cystatin C is highly correlated with creatinine ($r=0.6196$, $p<0.0001$). Prevalence of stage 3 CKD when GFR is estimated by the MDRD equation study is 17.2 %, which is significantly and much higher than the prevalence obtained when cystatin C-based equations are used. Indeed, prevalence is 2 %, 3.3 % and 5.8 % with the Levey 1, 2 and 3 equations, respectively. **Conclusions.** The prevalence of stage 3 CKD varies strongly following the method used for estimating GFR, creatinine-based or cystatin C-based equations. Such discrepancies must be confirmed and explained in additional studies using GFR measured with a reference method.

Keywords: Chronic kidney disease; creatinine; cystatin C; glomerular filtration rate

Introduction

The prevalence of end-stage renal failure is increasing in Western countries [1] and, in this context, prevention of chronic kidney disease (CKD) is important [2]. The first step for efficient prevention is early diagnosis, but serum creatinine is of limited value for such a task, as it is known that creatinine will rise above normal values only when 50 % of glomerular filtration rate (GFR) has already been lost [3,4]. Limitations of serum creatinine are numerous, but its lack of sensitivity is due especially to its relationship with muscular mass. Creatinine therefore lacks sensitivity in populations with lower muscular mass, notably the older population [4,5]. Several authors have proposed a creatinine-based equation to improve GFR estimation. Today, the modification of diet in renal disease (MDRD) study equation is the one most used for estimating GFR and has succeeded the older Cockcroft equation [6]. Recent epidemiological data have shown that nearly 10 % of the population in the USA have stage 3 CKD or worse, defined as estimated GFR lower than 60 mL/min/1.73 m². These results were obtained with

the MDRD study equation [1]. However, we and others have emphasized that the MDRD equation is neither accurate nor precise in estimating GFR in healthy populations and, more obviously, when it is applied to normal creatinine values [7–9]. There are several good reasons for believing that the MDRD study equation underestimates GFR (and thus overestimates CKD prevalence) in populations with normal or near-normal creatinine values [7,8].

Plasma cystatin C is a relatively new marker of GFR. Indeed, although strong physiological studies are few in number, cystatin C is constantly produced by all nucleated cells of the body, freely filtrated through the glomeruli and neither reabsorbed nor secreted by the tubules. It is fully catabolized in the proximal tubules [10–12]. Cystatin C has been shown of interest in the early detection of decreased kidney function. Moreover, several equations based on cystatin C level have been built to estimate GFR. However, most have been elaborated from a limited sample and have been poorly validated [10,12]. Recently, Levey's group, which is at the origin of the MDRD study equation, has elaborated three

cystatin C-based equations with different variables from a large sample of CKD patients ($n=2980$): Levey 1 with cystatin C as the only variable, Levey 2 including cystatin C, age, sex and race as variable and Levey 3 including these same variables and the serum creatinine [13]. It has been interesting to evaluate the prevalence of CKD (defined as estimated GFR under 60 mL/min/1.73 m²) with the MDRD study equation, on the one hand, and with these three new cystatin C-based equations, on the other.

Method

This retrospective study was driven in the context of the CKD screening programme organized by the Province of Liège's Health deputation. The Province of Liège, one of the 10 provinces in Belgium, covers an area of 3862 km² and its population from 2005 data has been calculated at 1,037,161 inhabitants. CKD screening is organized by participants visiting a mobile medical unit travelling through the 84 communes of the Province. On a voluntary basis, people aged between 45 and 75 years are invited for screening. Blood samples and anthropometrical data are collected and a short interview is carried out. The blood samples are sent frozen to the Clinical Chemistry Laboratory of the University of Liège within the following 24 h. Between September and December 2006, all the samples were frozen at -20°C and in January and February 2008 they were thawed. Serum creatinine was measured by the IDMS traceable enzymatic method from Roche (Crea plus; Roche Diagnostics, Mannheim, Germany) on a Hitachi 917. For creatinine determination, our laboratory has been enrolled in different external quality assessments, such as the Belgian IPH (Institute of Public Health) and German DGKL (Deutsche Gesellschaft für Klinische Chemie und Laboratoriumsmedizin). This assay is also currently accredited against the ISO 15189 Standard. Cystatin C was measured by particle-enhanced nephelometric immunoassay (PENIA) on the BNII nephelometer (Siemens Healthcare Diagnostics, ex-Dade-Behring, Marburg, Germany). This PENIA assay is the same as the one that Levey et al. used in their study. The equations are given in Table I. As our creatinine is IDMS traceable, we used the new "175" MDRD study equation [6].

A random spot urine was obtained and proteinuria was researched by dipstick analysis (Combur³; Roche Diagnostics, Mannheim, Germany). Hypertension and diabetes were self-reported by the participants.

As the distribution of estimated GFRs by creatinine-based equations is not normal, the

Table I. Creatinine-based (S Cr; mg/dL) and cystatin C-based (CC; mg/L) equations for estimating glomerular filtration rate (GFR).

<i>4-variable MDRD Study equation</i>	
GFR (mL/min/1.73 m ²)	$=175 \times \text{SCr (mg/dL)}^{-1.154} \times \text{Age}^{-0.203} \times 0.742 \text{ (if woman)} \times 1.21 \text{ (if black)}$
<i>Levey 1 equation</i>	
GFR (mL/min/1.73 m ²)	$=76.7 \times \text{CC (mg/L)}^{-1.19}$
<i>Levey 2 equation</i>	
GFR (mL/min/1.73 m ²)	$=127.7 \times \text{CC (mg/L)}^{-1.17} \times \text{Age}^{-0.13} \times 0.91 \text{ (if woman)} \times 1.06 \text{ (if black)}$
<i>Levey 3 equation</i>	
GFR (mL/min/1.73 m ²)	$=177.6 \times \text{SCr (mg/dL)}^{-0.65} \times \text{CC (mg/L)}^{-0.57} \times \text{Age}^{-0.2} \times 0.82 \text{ (if woman)} \times 1.11 \text{ (if black)}$

different results of estimated GFR were compared using the Wilcoxon test. We calculated and compared the percentage of patients with stage 3 CKD or worse (stage 3 CKD being defined as an estimated GFR under 60 mL/min/1.73 m²) obtained with the four equations, and the coefficients of correlation between the different equations were calculated. Agreement between equations to discriminate GFR above and below 60 mL/min/1.73 m² was evaluated by Kappa statistics. We also compared the results of GFR estimated by the MDRD study equation, on the one hand, and the results of GFR estimated by the cystatin C-based equations, on the other, by Bland and Altman analysis [14]. In these analyses, we arbitrarily chose the creatinine-based equation results as the referent. As cystatin C is not (or very little) dependent on muscular mass, we specifically studied a subgroup of patients based on body mass index (> or <30 kg/m²). Bias between equations was defined as the mean of the differences. The SD around the mean reflects the dispersion and precision of the equations. $P < 0.05$ was considered as significant. All analyses were performed using MedCalc[®] (MedCalc Software; Mariakerke, Belgium).

Results

During the study period, 754 people were screened (48.7 % male and 51.3 % female). The anthropometric, clinical and biological characteristics of the global population are given in Table II. There is no difference between men and women in relation to anthropometrical and clinical data, nor are mean creatinine and cystatin C different between the sexes. As the Levey 1 equation does not include a sex factor correction, there is logically no difference between the mean values obtained with this equation in men and women. However, mean estimated GFR is

Table II. Anthropometric and biological description of the population ($n=754$). Data are expressed as mean \pm SD.

$N=754$	Mean	SD
Age	61.3	8.6
Weight (kg)	74.7	14.7
Height (cm)	167	9
BMI (kg/m^2)	26.6	4.3
Current smokers (%)	23.6	
Diabetes (%)	12.8	
Hypertension (%)	31.7	
Proteinuria (%)	18	
Creatinine (mg/dL)	0.86	0.2
Cystatin C (mg/L)	0.76	0.16
MDRD study ($\text{mL}/\text{min}/1.73 \text{ m}^2$)	83	26
Levey 1	109	23
Levey 2	101	23
Levey 3	95	24

significantly different between the sexes (and lower in women) when the MDRD study equations are analysed (97 ± 24 versus $72 \pm 28 \text{ mL}/\text{min}/1.73 \text{ m}^2$), the Levey 2 (106 ± 24 versus $96 \pm 20 \text{ mL}/\text{min}/1.73 \text{ m}^2$) and the Levey 3 (105 ± 24 versus $86 \pm 20 \text{ mL}/\text{min}/1.73 \text{ m}^2$).

Cystatin C is highly correlated with creatinine ($r=0.6216$, $p<0.0001$). Plasma cystatin C and serum creatinine are correlated with age in our population ($p<0.0001$), correlation being significantly higher for cystatin C than for creatinine ($r=0.4096$ and $r=0.1960$, respectively).

With the Wilcoxon test, all the estimated GFRs are different from each other ($p<0.0001$). The prevalence of stage 3 CKD when GFR is estimated by the MDRD equation study is 17.2 %. This prevalence is significantly much higher than that obtained when cystatin C-based equations are used. Indeed, the prevalences of stage 3 CKD are 2 % and 3.3 % with the Levey 1 and 2 equations, respectively (no difference between these two equations). The prevalence of stage 3 CKD with the combined (creatinine and cystatin C) Levey 3 equation is significantly (5.8 %) lower than with the MDRD study equation, but significantly higher than with the Levey 1 and 2 equations. Kappa statistics show poor agreement between creatinine-based and cystatin C-based equations for discriminating GFR under and over $60 \text{ mL}/\text{min}/1.73 \text{ m}^2$ ($\kappa<0.2$).

All equation results are highly correlated ($p<0.0001$). The coefficients of correlation between the equations are given in Table III. All the correlations are statistically different, with the best correlation logically seen between the Levey 1 and 2 equation results and the weakest between the MDRD study and the Levey 1 study equation results.

Table III. Correlation between creatinine-based and cystatin C-based equations.

	MDRD study	Levey 1	Levey 2
MDRD Study			
Levey 1	0.51		
Levey 2	0.61	0.97	
Levey 3	0.93	0.78	0.85

The Bland and Altman analysis results are summarized in Figure 1. The mean difference between the MDRD study equation and the Levey 1 equation is $+25.3 \pm 24.2 \text{ mL}/\text{min}/1.73 \text{ m}^2$. The differences with the Levey 2 and 3 equations are $+17.4 \pm 21.5$ and $+11.9 \pm 9.5 \text{ mL}/\text{min}/1.73 \text{ m}^2$, respectively. The difference between the Levey 3 equations and the MDRD study equation is lower than the difference between the MDRD study equation and the other two Levey equations.

In the subgroup analysis based on the BMI, we show that the prevalence of CKD stage 3 is not different in the obese population whatever equation is used. In this specific subgroup ($n=148$), the mean eGFR by the MDRD study equation is not different from the global population (85 ± 26 versus $83 \pm 26 \text{ mL}/\text{min}/1.73 \text{ m}^2$, respectively). This is also the case for the Levey 3 equation (93 ± 24 versus $95 \pm 24 \text{ mL}/\text{min}/1.73 \text{ m}^2$, respectively). However, for the Levey 1 and 2 equations, the results of eGFR are significantly lower in the obese population than in the global population (Levey 1: 101 ± 22 versus $109 \pm 23 \text{ mL}/\text{min}/1.73 \text{ m}^2$, respectively, Levey 2: 95 ± 22 versus $101 \pm 23 \text{ mL}/\text{min}/1.73 \text{ m}^2$, respectively).

Discussion

Epidemiologic studies in different Western countries have recently shown that prevalence of CKD, defined as GFR under $60 \text{ mL}/\text{min}/1.73 \text{ m}^2$, is about 10 % in the global population [1,15]. These data have been obtained with the MDRD study equation using a well-calibrated serum creatinine [16,17]. However, the use of this equation is not free from criticism. We have recently demonstrated that this equation tends to underestimate GFR strongly in healthy populations and, more generally, in patients with normal or near normal creatinine values [7,8]. Cystatin C is thought to be a better marker of kidney function, especially because its concentration is less influenced by muscular mass than serum creatinine [12,18]. Several cystatin C-based equations have been proposed for estimating GFR and the recent cystatin C-based equations proposed by Levey et al. will certainly be the most successful in the future, because these three equations have been built from studies

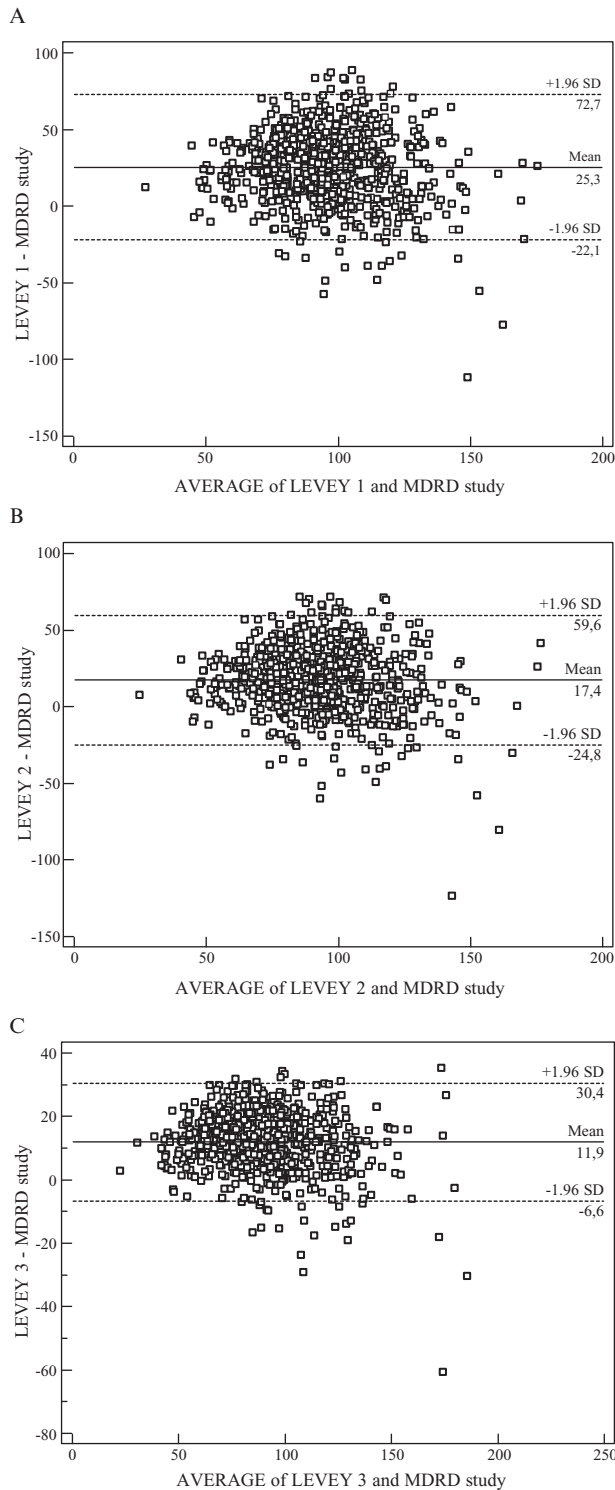


Figure 1. Bland and Altman analysis between the MDRD study equation and the three new Levey equations (A: Levey 1, B: Levey 2, C: Levey 3). The continuous line represents the mean difference between measured and estimated GFR, whereas the dashed lines represent the limits of agreement (mean difference \pm 2 SD). All values are expressed in mL/min/1.73 m².

with a large sample of patients [13]. In our population of volunteers, the prevalence of CKD is strongly discordant using creatinine-based or cystatin C-based equations. Indeed, if the prevalence of stage 3 CKD is as high as 17 % using the MDRD study equations, the prevalence will decrease to 2 %, 3.3 % and 5.8 % for the equations based on cystatin C concentrations only, on cystatin C, sex and age, and on cystatin C and creatinine concentrations sex and age, respectively. It seems logical to have a less important (although significant) difference between the results obtained with the MDRD and the Levey 3 equation than between the MDRD and the Levey 1 and 2 equations, as serum creatinine is part of the Levey 3 equation. From our point of view, and as other authors have also shown, the MDRD study equation underestimates GFR in healthy populations because this equation has been built from a CKD population (and the relationship between creatinine and GFR is not the same in healthy or in CKD patients) [9,19] and because the new factor 175 in the IDMS traceable equation has been obtained erroneously [7]. Moreover, the mean age of our study population is relatively high (61 ± 9 years) and the accuracy and precision of the MDRD study equation are probably still less in aged populations with low creatinine values [20]. Regarding the cystatin C-based equations, it may also be of interest to compare our population with the population where the three equations have been built. The population studied by Levey is a CKD population (mean GFR: 48 ± 25 mL/min/1.73 m²) [13]. However, contrary to creatinine, there is no reason to believe that the relationship between cystatin C and GFR is different in CKD and non-CKD populations. The Levey population is an American one and our subjects are European. The American Levey equation has still not been validated in a European population but, using another European built cystatin C equation [21] ($\text{eGFR} = 77.24 \times \text{CC (mg/L)}^{-1.2623}$), we found exactly the same prevalence of stage 3 CKD as with the Levey 1 equation (i.e. 1.99 %). Our population is also older than the Levey population (61 ± 9 years old versus 52 ± 13 years), but the influence of age seems of limited importance as there is no difference in the prevalence of our population using either the Levey 1 equation (using only cystatin C) or the Levey 2 equation (using cystatin C and age). Another point is that our population has a lower BMI than in the Levey population (27 ± 4 versus 29 ± 6 kg/m²). For some authors, cystatin C is not strictly independent of weight and muscular mass [18,22]. As cystatin C is higher in heavier patients, and as our patients are lighter than patients in the Levey study, the Levey equations should slightly underestimate GFR in our

population. The prevalence of stage 3 CKD with the cystatin C-based equations could theoretically still be overestimated in our population.

Obesity and age are both factors of risk for CKD [23]. However, no difference is found in stage 3 CKD prevalence when the creatinine-based equations (MDRD and Levey 3) are used between the global and the obese populations. On the other hand, the eGFR in the obese population is significantly lower with the cystatin C-based equations than in the global and non-obese population. This could be an indirect argument in favour of cystatin C-based equations, but the absence of true GFR measurement does not permit conclusions to be drawn.

The main limitation of our study is linked to the fact that we have not measured GFR with a reference method. So, even if we have indirect arguments affirming that MDRD study equations overestimate CKD prevalence in global populations, such an assertion can only be made if a reference method GFR is used. The new cystatin C-based equations must also be validated against measured GFR. In the same way, we are unable to confirm that the combined equation (Levey 3) is better for estimating GFR than the other two cystatin C-based equations. Our data only underline potential strong discrepancies between results in epidemiological studies when cystatin C-based or creatinine-based equations are used. Second, our stage 3 CKD prevalence data are of interest only because they illustrate these discrepancies. As our population is clearly not representative of the Belgian population (because only volunteers are included), our stage 3 CKD prevalence results cannot be considered epidemiologically. Thirdly, we have no data on ethnicity. As the ethnicity factor varies following the equations, this could be a source of bias. However, in Belgium, Caucasians are, by far, the dominant ethnic group. Moreover, there is little doubt that the differences observed in our study are not due to the ethnic factor (1.21 for the MDRD study equation, 1.06 and 1.11 for the Levey 2 and Levey 3 equations, respectively). Fourthly, plasma cystatin C concentration seems dependent on thyroid status and is influenced by steroid therapy independently of any GFR changes. These potential interferences have not been considered in our study [24,25]. Nevertheless, great discrepancies between creatinine and cystatin C-based results are certainly not fully explained by these potential interferences. Lastly, we have defined CKD as $\text{GFR} < 60 \text{ mL/min/1.73 m}^2$. The definition of CKD is subject to debate, however, notably in the elderly population [26]. Whatever, our data do not bring an end to this debate.

In conclusion, the present study illustrates large discrepancies in the prevalence of stage 3 CKD in a population according to the method used for estimating GFR (creatinine-based or cystatin C-based). We disfavour the MDRD study equations in epidemiological studies. More research is urgently needed to confirm and explain these discrepancies. Population studies using GFR measurements with a reference method are required.

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